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Title

Alemtuzumab versus natalizumab, fingolimod and interferon β for multiple sclerosis

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ABSTRACT

Background: Alemtuzumab, an anti-CD52 antibody, is proven to be more efficacious than interferon beta-1a in treating relapsing-remitting multiple sclerosis, but its efficacy relative to ~~other~~more potent immunotherapies is unknown.

Methods: We compared effectiveness of alemtuzumab vs. natalizumab, fingolimod and interferon β up to five years in propensity-matched patients with relapsing-remitting multiple sclerosis from MSBase and four other observational cohorts. Annualised relapse rates, disability ~~progression~~accumulation and disability ~~regression~~improvement events were compared with clustered weighted models. Secondary analyses examined patients with high pre-treatment relapse rate or on-treatment relapses.

ResultsFindings: The cohorts consisted of 189 (alemtuzumab), 2155 (interferon), 828 (fingolimod) and 1160 (natalizumab) patients. Compared to interferon, alemtuzumab was associated with lower annualised relapse rate (0.19 vs. 0.53, $P<0.001$), and similar disability outcomes in the overall cohort, and lower risk of disability ~~progression~~accumulation (hazard ratio=0.64, $P=0.018$) and a higher rate of disability ~~regression~~improvement in patients with prior highly active disease (hazard ratio=4, $P=0.03$). Compared to fingolimod, relapse rate was lower on alemtuzumab (0.15 vs. 0.34, $P<0.001$). Importantly, no differences in relapse rate (0.20 vs. 0.19, respectively, $P=0.78$) and disability ~~progression~~accumulation rates were found between alemtuzumab and natalizumab. Disability ~~regression~~improvement rates were lower on alemtuzumab (hazard ratio=0.36, $P<0.001$) than natalizumab, particularly during the first year after commencing therapy. The results were largely confirmed by four sensitivity analyses.

ConclusionsInterpretation: Alemtuzumab and natalizumab showed similar effects on relapse activity and disability ~~progression~~accumulation rates in relapsing-remitting multiple sclerosis but natalizumab was associated with a greater chance of early disability ~~regression~~improvement. Alemtuzumab was superior to fingolimod in mitigating relapse activity.

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TEXT

INTRODUCTION

Alemtuzumab, an anti-CD52 humanised monoclonal antibody, is a highly effective immunotherapy for relapsing-remitting multiple sclerosis (MS).¹⁻³ Through a profound pan-lymphocyte depletion and sustained modification of lymphocyte repertoire,⁴ it achieves long-term disease stabilisation in most patients with previously active disease.^{5,6} Pivotal trials have demonstrated its superior effect on relapse activity and disability accrual compared with interferon β .^{2,3}

Recent onset of highly active MS, escalation of therapy to natalizumab or alemtuzumab following failure of oral medications⁷ or switch from natalizumab to alemtuzumab or fingolimod due to a high risk of progressive multifocal leukoencephalopathy^{8,9} are common scenarios in which alemtuzumab is used in clinical practice. However, there is presently no information about the effectiveness of alemtuzumab in comparison to the ~~other~~ more potent disease modifying therapies. Mixed-treatment analyses of alemtuzumab versus other licensed agents were performed during submissions to reimbursement agencies (e.g. the National Institute for Health and Care Excellence, UK) but public versions of these documents are heavily redacted. This much needed evidence is unlikely to emerge from randomised trials as the cost of such long-term multi-arm trials is prohibitive.

Well characterised observational cohorts collect substantial amounts of longitudinal information representative of clinical practice. Several cohorts have recently generated valuable evidence regarding comparative treatment effectiveness, which is highly concordant with clinical trials.¹⁰ We have shown that in active MS, highly potent therapies, such as natalizumab or fingolimod, are more effective than injectable immunotherapies.^{11,12}

The present study compares relapse activity, disability ~~progression~~ accumulation and disability ~~regression~~ improvement between patients treated with alemtuzumab vs. other ~~potent~~ immunotherapies. First, we aimed to replicate the results of the pivotal trials of alemtuzumab vs. interferon β . Then, we explored the effectiveness of alemtuzumab in comparison with natalizumab or fingolimod over up to five years of treatment.

METHODS

The MSBase cohort study (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee, and by the site institutional review boards (or exemptions were granted, according to local regulations). Written informed consent was obtained from enrolled patients, as required.

Patients and follow-up

Longitudinal clinical data from 96 MSBase centres in 30 countries and patients treated with alemtuzumab from six MS centres in Cambridge,⁵ Cardiff, Bristol, Swansea,⁶ Dublin and Dresden¹³ were extracted between November 2015 and June 2016 and evaluated for inclusion criteria. These consisted of the following: definite relapsing-remitting MS,^{14,15} exposure to one of the study therapies, no prior exposure to hematopoietic stem cell transplantation, no participation in randomised clinical trials, minimum required recorded follow-up (12 months prior to treatment start and two on-treatment disability scores ≥ 6 months apart) and minimum dataset (consisting of sex, age, time of first MS symptom, dates of clinical relapses, clinical MS course, disability score at treatment commencement (-6 months to +3 months), ≥ 6 -month persistence on study therapy, ≥ 1 relapse experienced within the year before treatment, age ≤ 65

years, time from first MS symptom ≤ 10 years and Expanded Disability Status Scale (EDSS) score ≤ 6.5 .

Treatment protocols, which involved alemtuzumab (12-24mg i.v. daily for five days (cycle 1) or three days (cycle 2)), interferon β -1a (44 μ g s.c. thrice weekly), fingolimod (0.5mg oral daily) and natalizumab (300 μ g i.v. every four weeks) were described elsewhere.^{5,6,11} Baseline was defined as the first commencement of the study therapy and patients were censored at discontinuing therapy, commencing the first post-baseline disease modifying therapy or at the last recorded EDSS, whichever occurred first.

The analysed data were recorded as part of quality clinical practice, mostly at tertiary MS centres, with data entry at the time of clinical visits. The MSBase protocol stipulates minimum annual updates of the minimum dataset, but patients with less frequent visits were not excluded. Data entry portals included iMed, MSBase online data entry system, PatientCare, MSDS or local data entry systems. Rigorous quality assurance procedure was applied (Table S2).¹⁶

Study endpoints

The primary endpoint was the on-treatment annualised relapse rate. Secondary endpoints consisted of the cumulative hazard of relapses, disability progression accumulation events and disability regression improvement events.

A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for ≥ 24 hours, in the absence of concurrent illness/fever, and occurring ≥ 30 days after a previous relapse. Confirmation of relapses by EDSS was not required. Individual annualised relapse rate between baseline and censoring was calculated.

Disability was scored by accredited EDSS scorers (Neurostatus certification was required at the participating centres), excluding any score recorded within 30 days of a previous relapse. The definitions of disability progression accumulation and regression improvement required confirmation over ≥ 6 months, as described elsewhere.¹⁷

Matching and statistical analysis

Matching and statistical analysis were conducted using R (version 3.0.3)¹⁸, in three separate paired matched analyses of alemtuzumab vs. interferon β , fingolimod or natalizumab. Individual Ppatients were matched on their propensity of receiving either of the compared therapies.^{12,19} Individual propensity scores were calculated using a multivariable logistic regression improvement model of treatment allocation that utilised demographic and clinical variables available at the time of treatment assignment as independent variables: sex, age, time from first MS symptom, EDSS, number of relapses in the prior 12 months, number of prior MS therapies, and the perceived most effective prior MS therapy.

Patients were matched in a variable 2:1 ratio using nearest neighbour matching within a narrow caliper (0.1 standard deviations of the propensity score), without replacement. All subsequent analyses were designed as paired models with weighting to adjust for the variable matching ratio. A maximum cumulative weight for each matched patient was 1. The common on-treatment follow-up was determined in each matched pair as the shorter of the two patient follow-up periods (pairwise censoring), in order to control attrition bias.¹⁰

Tests of statistical inference were carried out at $\alpha=0.05$ with familywise Benjamini-Hochberg correction for false discovery rate. After assessing normality of data distribution, annualised relapse rates were compared with a weighted negative

binomial model with cluster effect for matched patient pairs and adjusted for visit frequency. Relapse rates at years 1-5 were compared with weighted paired t-tests. Cumulative hazards of relapses, EDSS progressionaccumulation and regressionimprovement events were analysed with weighted conditional proportional hazards models with robust estimation of variance (Andersen-Gill) adjusted for visit frequency. The proportions of patients free from relapse, EDSS progressionaccumulation and with EDSS regressionimprovement were evaluated with weighted conditional proportional hazards models (Cox) adjusted for visit frequency. Where the Pproportionality of hazards assumption was violated (assessed with Schoenfeld's global test), interaction term for treatment and time was included in the multivariable models.

Robustness of the statistically significant differences to unidentified confounders was quantified with Hodges-Lehmann Γ .²⁰ Where no statistically significant differences were observed, analytical power was quantified as the minimum effect magnitude detectable within the available cohort at $1-\beta=0.8$ using simulations ($n=200$).

Secondary and sensitivity analyses

Two secondary analyses and four sensitivity analyses were completed. The secondary analyses compared the therapies (i) among patients with high pre-baseline relapse activity (defined as ≥ 2 relapses within 12 months or ≥ 3 relapses within 24 months pre-baseline, irrespective of treatment status) and (ii) any prior on-treatment break-through relapses. The former used a 10:1 variable matching ratio in order to maximise analytical power. The sensitivity analyses evaluated the robustness of the results to potential confounders, including matching (using 10:1 variable matching within a caliper of 0.4), pre-baseline follow-up (matching on the number of relapses in the prior 24 months), MS phenotype (allowing inclusion of patients with secondary progressive MS), follow-up duration (including patients with ≥ 2 -year on-treatment follow-up) and confirmation of EDSS progressionaccumulation/regressionimprovement events over ≥ 12 months.

Role of the funding source

The study (including study design, the collection, analysis, and interpretation of data, writing of the report, and in the decision to submit the paper for publication) was conducted separately and apart from the guidance of the sponsors.

RESULTS

A total of 189, 2155, 828 and 1160 patients fulfilling the inclusion criteria and treated with alemtuzumab (from 1999), interferon β (from 1994), fingolimod (from 2010) and natalizumab (from 2006) were identified, respectively (Figure 1, Table S3). One hundred and five (55%) patients treated with alemtuzumab received two treatment cycles and 84 patients (45%) required additional treatment cycles. As expected, the four unmatched groups differed in their baseline characteristics (Table S4). As shown by the logistic regression models used to calculate propensity scores, patients commenced alemtuzumab earlier after their first MS presentation, at a younger age, and tended to have higher EDSS scores and pre-baseline relapse activity compared to the three other therapies (Table S5).

The numbers of patients retained in the matched cohorts for all three pairwise primary analyses are shown in Table 1. The matching procedure significantly decreased the between-group differences in propensity scores from 0.24-0.44 to 0.0001-0.0026, corresponding to a >99.4% improvement in the balance between the compared

groups. This is reflected by their close match on individual characteristics with standardised differences of $\leq 15\%$ (Table 1). The median differences between baseline date and the date of the baseline EDSS were comparable between the matched cohorts (-14-0 days [quartiles -71 to +12], standardised difference 0.02-0.19). As a result of pairwise censoring, on-treatment follow-up was identical in the matched groups. The groups were not matched on the follow-up visit density, therefore all subsequent analyses were adjusted for visit frequency.

Patients treated with alemtuzumab experienced a lower annualised relapse rate compared with interferon β (mean [95% confidence intervals] 0.19 [0.14-0.23] vs. 0.53 [0.46-0.61], respectively, $P < 0.001$; Figure 2). While a consistent decline in the relapse rate was observed in the interferon β group over the five years on treatment (representing time-dependent decline in relapse activity²¹), the difference between the groups remained significant throughout the follow-up. Cumulative hazard of relapse events was lower in the alemtuzumab group (hazard ratio 0.60, $P = 0.005$). The primary analysis did not show any differences in the cumulative hazards of disability progression/accumulation or regression/improvement ($P \geq 0.66$). However, the secondary analyses (in addition to confirming the differences in relapse outcomes) showed that alemtuzumab was associated with a lower hazard of disability progression/accumulation than interferon β in patients with high pre-baseline relapse activity and higher probability of disability regression/improvement in patients with previous on-treatment break-through relapses (Table S6).

Similarly, patients treated with alemtuzumab showed lower annualised relapse rate compared with fingolimod (mean [95% confidence intervals] 0.15 [0.10-0.20] vs. 0.34 [0.26-0.41], $P < 0.001$; Figure 3). This observation was consistent during years 1-3, for which sufficient cohorts were available. The difference in cumulative hazard of relapses failed to reach the level of statistical significance ($P = 0.18$). ~~More patients in the alemtuzumab group tended to remain free from relapses (hazard ratio 0.59, $P = 0.065$).~~ No between-group differences in the cumulative hazards of disability progression/accumulation or regression/improvement were observed.

The comparison between alemtuzumab and natalizumab showed similar on-treatment annualised relapse rates over four years (mean [95% confidence intervals] 0.20 [0.14-0.26] vs. 0.19 [0.15-0.23], $P = 0.78$; Figure 4), confirmed by equivalence in the cumulative hazard of relapses ($P = 0.83$) and probability of remaining relapse free ($P = 0.65$). Cumulative hazard of disability progression/accumulation events was also similar ($P = 0.60$). However, alemtuzumab was associated with lower cumulative probability of disability regression/improvement than natalizumab (hazard ratio 0.35, $P < 0.001$). This difference in disability outcomes was also confirmed among patients with high pre-baseline relapse activity.

Sensitivity analyses have confirmed the outcomes of the primary and secondary analyses (with the exception of disability outcomes in the comparison of alemtuzumab vs. interferon β). The comparisons of the rates of disability progression/accumulation and regression/improvement events confirmed over 6-months were also largely replicated in the sensitivity analysis requiring a 12-month confirmation interval. Modifying the matching ratio and caliper, pre-baseline observational period, inclusion of secondary progressive MS and minimum on-treatment follow-up did not significantly change the overall relapse and disability outcomes (see Table S6).

Where the primary analysis did not show any significant differences between the compared groups, analysis of the minimum detectable effect size was carried out (Table S7). The analyses were sufficiently powered to detect minimum differences of 0.13 relapse per year, 51-53% cumulative hazard of relapses, 35-66% cumulative hazard of disability progression/accumulation and 39-42% cumulative probability of

disability ~~regression~~improvement. The differences in annualised relapse rates observed for alemtuzumab vs. interferon β and fingolimod were resistant to unknown confounders with relative magnitudes of >100% and 60% of the reported effect of treatment (Hodges-Lehmann Γ), respectively.

DISCUSSION

In this large combined observational propensity score-matched study of patients with relapsing-remitting multiple sclerosis, alemtuzumab and natalizumab were equally effective in reducing relapse frequency and preventing confirmed disability ~~progression~~accumulation over four years. However, natalizumab was more likely to lead to disability ~~regression~~improvement, particularly during the first year after commencing therapy. Compared to fingolimod, alemtuzumab was superior in reducing relapse activity. ~~No differences were found between alemtuzumab and fingolimod and comparable in their ability to~~modulating the risk of disability ~~progression~~accumulation or ~~regression~~improvement events over three years.

In order to enable interpretation of these results in the context of the original pivotal clinical trials, we have first conducted a comparison of alemtuzumab vs. high-dose interferon β -1a. This study has partially replicated the results of these pivotal trials ~~comparing the effect of alemtuzumab to high-dose interferon β -1a~~: alemtuzumab is superior to interferon β in suppressing relapse activity and reducing disability accrual in patients with previously highly active MS. The observed on-treatment annualised relapse rates (0.19 vs. 0.53, alemtuzumab vs. interferon β , respectively) are comparable to the relapse rates reported by the CAMMS223 (0.16 vs. 0.54), CARE-MS1 (0.18 vs. 0.39) and CARE-MS2 (0.26 vs. 0.52) trials. The proportion of patients who experienced 6-month confirmed ~~progression~~accumulation of disability at two years was similar between the present study (7% vs. 12%, alemtuzumab vs. interferon β , respectively) and the CARE-MS1 trial (8% vs. 11%), with neither being significantly different. However there was a treatment effect on disability ~~progression~~accumulation events in the CAMMS223 (6% vs. 16%) and CARE-MS2 (13% vs. 20%) trials at two years. It should be noted that the cohorts are not directly comparable; the alemtuzumab trials recruited patients with ≥ 2 relapses during the preceding two years, while inclusion into our primary analysis was based on ≥ 1 relapse during the preceding one year. Our secondary analyses, which only included patients with high pre-baseline activity (≥ 2 relapses during the one year or ≥ 3 relapses during the two years pre-baseline) and previous break-through on-treatment relapses showed improved disability outcomes in alemtuzumab compared with interferon β (decreased cumulative hazard of disability ~~progression~~accumulation and increased probability of disability ~~regression~~improvement, respectively). Thus, our results from patients with highly active MS are concordant with those produced in the relevant comparative alemtuzumab versus interferon β trials.

The on-treatment annualised relapse rates observed in the natalizumab and fingolimod groups (0.19 and 0.34, respectively) are in keeping with the previously reported on-treatment MS activity from MSBase^{11,12} and the pivotal trials for natalizumab (0.20-0.24)²² and are higher than the annualised relapse rates reported in the pivotal trials for fingolimod and (0.186-0.420)^{23,24}. In keeping with our previous observation of superior control of disease activity after escalating therapy to natalizumab compared with fingolimod, alemtuzumab was comparable to natalizumab but superior to fingolimod in preventing MS relapses. Both effects were sustained over at least 3-4 years following the commencement of therapy. While the hazard of disability ~~progression~~accumulation was similar for alemtuzumab and both natalizumab and

fingolimod, treatment with natalizumab increased the probability of confirmed disability ~~regression~~improvement more than alemtuzumab. This extends prior observations that natalizumab, unlike fingolimod, is likely to increase the probability of partial recovery from the previously accumulated neurological disability, in particular during the initial years after first MS presentation.^{12,25}

In the present study, we maximised analytical power by combining several high-quality longitudinal observational MS cohorts.^{5,6} Cumulative follow-up and generalisability were maximised by inclusion of a broad spectrum of patients with the minimum follow-up requirements necessary to evaluate confirmed disability outcomes. Both, treatment-naïve patients and patients previously exposed to immunotherapies were included. Because the assembled study cohort is, by definition, multicentric, we have undertaken multiple steps to mitigate the potential biases, including matching, pairwise censoring and adjusting the statistical models,¹⁰ an approach whose efficacy was demonstrated in our previous studies.^{11,12} The alemtuzumab cohorts were enriched for patients with early, highly active disease. Given the large number of patients treated with natalizumab, fingolimod or interferon β available from the MSBase cohort, we were able to achieve close match on their demographic and clinical characteristics. Because the probability of capturing treatment discontinuation was relatively lower in the alemtuzumab cohort, we have mitigated the risk of differential follow-up duration by pairwise censoring. ~~In addition, we have shown that the results were robust to hypothetical unidentified confounders.~~ It is arguable that our approach was underpowered to detect some clinically significant treatment effects.

A-The main limitation~~weakness~~, in comparison to controlled studies, is the lack of systematic and comparable acquisition of safety data and of radiological outcomes. Magnetic resonance imaging is an important indicator of subclinical disease activity, with potential impact on disease management. If unreported and systematically different between the compared cohorts, it could represent an unidentified confounder. Another potential confounder is the effect of treating centre. Due to the limited overlap between the centres reporting patients treated with alemtuzumab and the three comparator therapies, we were not able to match on or adjust for centre, but we have mitigated the effect by adjusting the analyses for visit frequency, which served as an indicator of follow-up density. In addition, wImportantly, we have shown that the our results were robust to hypothetical unidentified confounders of the magnitude >60% of the difference in treatment effects. The definition of MS relapses used in our study did not require confirmation by change in EDSS, which reflects usual clinical practice; this was different from several clinical trials which required EDSS confirmation. This study compared treatment outcomes in observational data over 3-5 years. It is worth noting that disability accumulation events confirmed over 6-12 months are highly indicative of long-term disability outcomes.¹⁷ Comparative evaluation of the long-term safety of alemtuzumab and natalizumab is ~~therefore~~ warranted, as treatment safety represents an important component of disease management strategy.

In conclusion, we show that - over ~~four~~three to five years - alemtuzumab is a highly effective disease modifying therapy in relapsing-remitting MS, with a treatment effect largely comparable to natalizumab, and with greater effect on relapse rate than fingolimod or interferon β -1a.

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The list of MSBase Study Group co-investigators and contributors is given in **Table S1**.

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DECLARATION OF INTERESTS

Tomas Kalincik served on scientific advisory boards for Roche, Genzyme-Sanofi, Novartis, Merck and Biogen, has received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanofi, Teva, BioCSL and Merck and has received research support from Biogen.

James William Lyle Brown has received travel expenses from Novartis and Sanofi-Genzyme.

Neil Robertson has received lecture honoraria and consultancy fees from Biogen, Genzyme, and Novartis and has received research funding from Novartis and Genzyme.

Mark Willis did not disclose any conflict of interests.

Neil Scolding has received research support from Biogen, Sanofi-Genzyme, Merck-Serono and Teva.

Claire M Rice did not disclose any conflict of interests.

Alastair Wilkins did not disclose any conflict of interests.

Owen Pearson received honoraria and support to attend scientific meetings, speakers' fees, and advisory boards from Biogen, Genzyme, Novartis, Teva, Merck Serono and Roche.

Tjalf Ziemssen has received compensation for consulting services from Almirall, Biogen Idec, Bayer, Genzyme, GlaxoSmithKline, MSD, Merck Serono, Novartis, Sanofi, Teva, and Synthon, and has received research support from Bayer, Biogen Idec, the Hertie Foundation, the Roland Ernst Foundation, the German Diabetes Foundation, Merck Serono, Novartis, Teva, and Sanofi Aventis. Further, he is a lead investigator in the PANGAEA and PEARL study.

Michael Hutchinson served on a medical advisory board for the CONFIRM study [BG00012] for Biogen-Idec, serves on the editorial board of the Multiple Sclerosis journal, has received speaker's honoraria from Novartis, Biogen Idec and Bayer-Schering and receives research support from Dystonia Ireland, the Health Research Board of Ireland and the European Dystonia Foundation.

Christopher McGuigan has received research grants from Biogen, Genzyme, Novartis, Teva, Bayer and honoraria as a consultant from Biogen, Genzyme, Novartis and Roche.

Vilija Jokubaitis received conference travel support from Novartis and Merck Serono and speaker honoraria from Biogen.

Tim Spelman received honoraria for consultancy, funding for travel and compensation for serving on scientific advisory boards from Biogen and speaker honoraria from Novartis.

Dana Horakova received speaker honoraria and consulting fees from Biogen, Merck Serono, Teva and Novartis, as well as support for research activities from Biogen and research grants from Charles University in Prague (PRVOUK-P26/LF1/4 and Czech Ministry of Health (NT13237-4/2012).

Eva Havrdova received speaker honoraria and consultant fees from Biogen, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen, Merck Serono and research grants from Charles University in Prague (PRVOUK-P26/LF1/4 and Czech Ministry of Health (NT13237-4/2012).

Maria Trojano received speaker honoraria from Biogen-Idec, Bayer-Schering, Sanofi Aventis, Merck-Serono, Teva, Novartis and Almirall; has received research grants for her Institution from Biogen-Idec, Merck-Serono, and Novartis.

Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck Serono and Teva.

Alessandra Lugaresi is a Bayer, Biogen, Genzyme, Merck Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla (FISM). Her institution received research grants from Bayer, Biogen, Merck, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla (FISM).

Alexandre Prat did not declare any competing interests.

Marc Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD Serono. He has also received a research grant from Canadian Institutes of Health Research.

Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD Serono, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.

Pierre Grammond is a Novartis, Teva-neuroscience, Biogen and Genzyme advisory board member, consultant for Merck Serono, received payments for lectures by Merck Serono, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis.

Raed Alroughani received honoraria from Biologix, Biogen, Bayer, Genpharm, Genzyme, Merck-Serono, GSK and Novartis, and served on advisory board for Biologix, Biogen, Bayer, Genpharm, Genzyme, Novartis, Genzyme, Merck-Serono and Novartis.

Eugenio Pucci served on scientific advisory boards for Merck Serono, Genzyme and Biogen; he has received honoraria and travel grants from Sanofi Aventis, UCB, Lundbeck, Novartis, Bayer Schering, Biogen, Merck Serono, Genzyme and Teva; he has received travel grants and equipment from "Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche".

Patrizia Sola served on scientific advisory boards for Biogen Idec and TEVA, she has received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, Teva, Sanofi Genzyme, Novartis and Bayer and research grants for her Institution from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva.

Raymond Hupperts received honoraria as consultant on scientific advisory boards from Merck-Serono, Biogen, Genzyme-Sanofi and Teva, research funding from Merck-Serono and Biogen, and speaker honoraria from Sanofi-Genzyme and Novartis.

Jeannette Lechner-Scott accepted travel compensation from Novartis, Biogen and Merck. Her institution receives the honoraria for talks and advisory board commitment from Bayer Health Care, Biogen, Genzyme Sanofi, Merck, Novartis and Teva, has been involved in clinical trials with Biogen, Novartis and Teva.

Murat Terzi received travel grants from Merck Serono, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Vincent Van Pesch received travel grants from Biogen, Bayer Schering, Genzyme, Merck, Teva and Novartis Pharma. His institution receives honoraria for consultancy and lectures from Biogen, Bayer Schering, Genzyme, Merck, Roche, Teva and Novartis Pharma as well as research grants from Novartis Pharma and Bayer Schering.

Csilla Rozsa received speaker honoraria from Bayer Schering, Novartis and Biogen, congress and travel expense compensations from Biogen, Teva, Merck Serono and Bayer Schering.

Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals.

Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Franco Granella served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Almirall.

Mark Slee has participated in, but not received honoraria for, advisory board activity for Biogen, Merck Serono, Bayer Schering, Sanofi Aventis and Novartis.

Daniele Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck-Serono.

Javier Olascoaga serves on scientific advisory boards for Biogen, Genzyme and Novartis; has received speaker honoraria from Biogen, Bayer-Schering, Genzyme, Merck-Serono, Novartis and Teva and research grants from Biogen, Merck Serono, Novartis and Teva.

Roberto Bergamaschi received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva; research grants from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi-Aventis, Teva; congress and travel/accommodation expense compensations by Almirall, Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva.

Freek Verheul is an advisory board member for Teva Biogen Merck Serono and Novartis.

Steve Vucic did not declare any competing interests.

Pamela McCombe did not declare any competing interests.

Suzanne Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering.

Jose Luis Sanchez-Menoyo accepted travel compensation from Novartis and Biogen, speaking honoraria from Biogen, Novartis, Sanofi, Merck Serono, Almirall, Bayer and Teva and has participated in a clinical trial by Biogen.

Radek Ampapa received conference travel support from Novartis, Teva, Biogen, Bayer and Merck Serono and has participated in a clinical trials by Biogen, Novartis, Teva and Actelion.

Magdolna Simo received speaker honoraria from Novartis, Biogen, Bayer Schering; congress/travel compensation from Teva, Biogen, Merck Serono, Bayer Schering.

Tunde Csepany received speaker honoraria/ conference travel support from Bayer Schering, Biogen, Merck Serono, Novartis and Teva.

Cristina Ramo received research funding, compensation for travel or speaker honoraria from Biogen, Novartis, Genzyme and Almirall.

Edgardo Cristiano received honoraria as consultant on scientific advisory boards by Biogen, Bayer-Schering, Merck-Serono, Genzyme and Novartis; has participated in clinical trials/other research projects by Merck-Serono, Roche and Novartis.

Michael Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck-Serono and Novartis.

Helmut Butzkueven served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck Serono, Novartis and Biogen.

Alasdair Coles has received consulting and lecture fees from Genzyme-Sanofi, lecture fees from Merck Serono and research support paid to his institution from Genzyme-Sanofi.

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RESEARCH IN CONTEXT

Evidence before this study

Alemtuzumab, is a highly effective therapy for multiple sclerosis. Similar to natalizumab, another highly effective multiple sclerosis therapy, it has shown an effective control of multiple sclerosis activity and reduction in disability accrual. In a number of scenarios, clinicians and their patients are faced with the decision between alemtuzumab or natalizumab (such as early active treatment in aggressive multiple sclerosis, escalation of therapy following failure of other therapies or switch from natalizumab to alemtuzumab due to a high risk of natalizumab-associated serious adverse events). No evidence comparing the efficacy of alemtuzumab and natalizumab is available to guide these clinical decisions.

Added value of this study

This study provides a conclusive evidence comparing effectiveness of alemtuzumab vs. natalizumab and fingolimod (another novel immunotherapy) for multiple sclerosis. Alemtuzumab and natalizumab show similar effects on relapse activity and disability ~~progression~~accumulation but natalizumab is associated with a greater chance of early disability reduction. Alemtuzumab is superior to fingolimod in mitigating relapse activity.

Implications of all the available evidence

While alemtuzumab is superior in controlling multiple sclerosis activity relative to fingolimod, its efficacy is largely comparable to that of natalizumab. Therefore, treatment decisions between alemtuzumab and natalizumab should be primarily governed by the therapies' safety profiles.

FIGURE LEGENDS

Figure 1

CONSORT diagram of patient disposition

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis

Figure 2

Comparison of the treatment outcomes for alemtuzumab vs. interferon β

Figure 3

Comparison of the treatment outcomes for alemtuzumab vs. fingolimod

Figure 4

Comparison of the treatment outcomes for alemtuzumab vs. natalizumab

Table 1

Characteristics of the matched patient groups at baseline

	alemtuzumab	interferon β	d	alemtuzumab	fingolimod	d	alemtuzumab	natalizumab	d
patients, nr (% female)	124 (73%)	218 (74%)		114 (72%)	195 (73%)		138 (70%)	223 (66%)	
age, yr, mean \pm SD	33 \pm 8	33 \pm 9	0.01	33 \pm 8	34 \pm 10	0.09	33 \pm 9	33 \pm 10	0.02
disease duration, yr, median (quartiles)	3.2 (2.6-2)	2.6 (1.2-6.4)	0.01	3.9 (2.4-6.6)	4.2 (1.6-8.1)	0.13	3.3 (2.1-6.3)	2.7 (1.7-6)	0.13
relapses 12 months pre- baseline, mean \pm SD	2 \pm 1.2	1.9 \pm 0.9	0.06	1.8 \pm 1.1	1.7 \pm 0.8	0.03	2 \pm 1.3	2 \pm 1	0.03
disability, EDSS step, median (quartiles)	3 (2-4)	3 (2-4)	0.12	3 (1.6-4)	3 (1.5-4.5)	0.00	3 (2-4.5)	3 (2-4.5)	0.01
inter-visit interval, months, median (quartiles)	9 (7-13)	4 (2-7)	0.72	9 (6-12)	3 (2-5)	1.17	9 (6-12)	3 (1-5)	1.12
previous therapies, nr, median (quartiles)	0 (0-1)	0 (0-1)	0.01	1 (0-1)	1 (0-2)	0.11	0 (0-1)	0 (0-1)	0.15

most active previous therapy, patients										
Interferon β/Glatiramer acetate	31 (25%)	62 (28%)		46 (40%)	85 (44%)		47 (34%)	97 (43%)		
Teriflunomide	0	0		0	0		0	0		
Dimethyl fumarate	0	0		0	0		0	0		
Fingolimod	0	0		0	0		2 (1%)	4 (2%)		
Natalizumab	3 (2%)	4 (2%)		14 (12%)	22 (11%)		0	0		
Mitoxantrone	3 (2%)	4 (2%)		2 (2%)	5 (3%)		0	0		
other	0	0		0	0		0	0		
none	87 (70%)	148 (68%)		52 (46%)	83 (43%)		89 (64%)	122 (55%)		
post-baseline pairwise-censored follow-up on study therapy, yr, median (quartiles)	2.1 (1.0-3.9)	2.1 (1.0-3.9)	0.00	1.7 (1.1-2.3)	1.7 (1.1-2.3)	0.00	2.1 (1.4-3.4)	2.1 (1.4-3.4)	0.00	

d, standardised difference (Cohen's d); SD, standard deviation; EDSS, Expanded Disability Status Scale